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1c662 U.S. PTO

# UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. 1.53(b))

Attorney Docket No.

0198/053

First Named Inventor or Application Identifier

Sylvie Veriac et al.

Title

Reagent For Determination Of Leucocytes And  
Measurement Of Haemoglobin In A Sample Of  
Blood

Express Mail Label No.

## APPLICATION ELEMENTS

ADDRESS TO:

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1. ☒ Filing Fee as calculated below.
2. ☒ Specification [Total Pages **16**]  
(preferred arrangement set forth below)
  - Descriptive title of the invention
  - Cross References to Related Applications
  - Statement Regarding Fed sponsored R & D
  - Reference to Microfiche Appendix
  - Background of the Invention
  - Brief Summary of the invention
  - Brief Description of the Drawings (if filed)
  - Detailed Description
  - Claim(s)
  - Abstract of the Disclosure
3. ☒ Drawing(s) (35 USC 113) [Total Pages **2**]
4. ☐ Oath or Declaration [Total Pages **2**]
  - a. ☒ Newly executed (original or copy)
  - b. ☐ Copy from a prior application (37 CFR 1.63(d))  
(for continuation/divisional with Box 17 completed)
 

☐ **DELETION OF INVENTOR(S)**  
 Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b)
5. ☐ Incorporation By Reference (useable if Box 4b is checked) The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)
7. ☐ Nucleotide and/or Amino Acid Sequence
  - Submission (if applicable, all necessary)
    - a. ☐ Computer readable copy
    - b. ☐ Paper Copy (identical to computer copy)
    - c. ☐ Statement Verifying identity of above copies
8. ☒ Assignment papers (cover sheet & document(s))
9. ☐ 37 CFR 3.73(b) Statement ☒ Power of Attorney
10. ☐ English Translation Document (if applicable)
11. ☒ Information Disclosure ☒ Copies of IDS  
Statement (IDS)/PTO-1449 Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)  
(Should be specifically itemized)
14. ☐ Small Entity ☐ Statement filed in prior application,  
Statement(s) Status still proper and desired
15. ☒ Certified copy of Priority Document(s)  
(if foreign priority is claimed)
14. ☒ Other: Submission of Priority claim from France  
9903467 filed March 19, 1999 & French  
Search Report

17. If a **CONTINUING APPLICATION**, check appropriate box and supply the requisite information:

☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No. /

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# Fee Calculation and Transmittal

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	NO. FILED			NO. EXTRA	RATE	FEE		RATE	FEE
TOTAL	11	minus	20	= 0	x9=	\$		x18=	\$0
INDEP	1	minus	3	= 0	x39=	\$		x78=	\$0
First Presentation, Multiple Dependent Claims					+130=	\$		+260=	\$
Base Filing Fee						\$345			\$690
Other Fee (specify purpose) Assignment recordal						\$			\$40
TOTAL FILING FEE* (accounting for possible small entity status)						\$	OR TOTAL		\$730



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Name (Print/Type)	Burton A. Amerrick	Registration No. (Attorney/Agent)	24,852
Signature			Date 3-15-00

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Reagent for determination of leucocytes and measurement of haemoglobin in a sample of blood

**Background of the invention**

- 5 The invention relates to haematological analyses.

More particularly, it concerns a reagent for determination of leucocytes and measurement of haemoglobin in a sample of blood.

10

The invention also aims to provide such a reagent which permits a leucocytic subpopulation to be identified, in particular the basophil polymorphonuclear leucocytes.

- 15 The determination of leucocytes, in particular of certain leucocytic subpopulations, as well as the measurement of the haemoglobin concentration of the erythrocytes or red corpuscles are very important for diagnosis in human pathology.

20

It will be recalled here that the leucocytes, or human white corpuscles, are divided into five subpopulations, namely three main subpopulations: the lymphocytes, monocytes and polymorphonuclear leucocytes or granulocytes, 25 with the latter being themselves subdivided into neutrophils, eosinophils and basophils, according to the characteristics of their cytoplasmic granules.

- Determination of the total leucocytes as well as 30 identification of their various subpopulations are achieved by means of traditional techniques of microscopic observation or by more modern techniques, mainly based on the measurement of variations in resistivity (WO 84/03771) or on optical diffraction (US 3,740,143), which have been 35 developed for specific automatic appliances.

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For the identification of the leucocytic subpopulations the numeration of the basophil granulocytes is particularly tricky, considering that this population represents, in a healthy individual, only 0.5 % to 1 % of the total

5 leucocytic population.

An increase in this basophil population is observed, attaining a population of 2 to 3 % by weight, in the course of allergic reactions. Amongst the infections,

10 tuberculosis and varicella can bring about basophilia, as can myxoedema and hyperlipidaemias amongst the metabolic diseases. Consequently, numeration of the basophil granulocytes assumes particular importance.

15 Patent FR 90 01660 and its equivalent US 5,196,346 describe a reagent that preserves the basophil granulocytes in such a way so as to permit determination thereof by measurement of resistivity. However, this reagent does not permit the measurement of haemoglobin.

20 It will be recalled that haemoglobin is a chromoprotein contained in the red corpuscles of the blood or erythrocytes.

25 Measurement of the haemoglobin concentration therefore necessitates the use of a reagent for cellular lysis that is capable of causing lysis of the erythrocytes in order to liberate the haemoglobin for measurement thereof.

30 For this purpose it is known to use reagents containing at least one detergent and cyanide ions which are capable of carrying out conversion of the haemoglobin into a chromogenic compound in order to permit determination thereof by colorimetry measurement.

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A cyanic reagent of this type is described in patents US 3,874,852 and US 3,854,914.

However, these reagents have the principal drawback of using cyanide. Moreover, they do not permit identification and quantification of the leucocytic subpopulations contained in the sample of blood to be analysed.

It should be noted that reagents that do not contain cyanide and that permit determination of leucocytes in addition to measurement of haemoglobin have already been proposed in the prior art.

Thus document WO 96/02841 describes a reagent for measuring haemoglobin without cyanide, which contains a detergent as well as a salt of hydroxylamine. This reagent can be used for numeration of the total leucocytes, but no leucocytic differentiation is possible.

Patent US 5,242,832 describes a similar reagent which also permits partial leucocytic identification. However, this reagent does not permit identification of the basophil cells but permits solely evaluation of the lymphocytes, monocytes and granulocytes.

Document WO 98/32016 also describes a reagent of this type. However, the minority granulocytic subpopulations, namely the eosinophils and the basophils, are not identified by the reagent that is described in this publication.

#### Summary of the invention

The object of the invention is, notably, to overcome the drawbacks of the known reagents.

It aims, in particular, to provide a haematological-analysis reagent for the determination of leucocytes, and in particular for the identification and quantification of a leucocytic subpopulation constituted by the basophil cells, in a sample of whole blood.

The invention also aims to provide a reagent that permits, notably, lysis of the erythrocytes or red corpuscles, which is necessary for determination of leucocytes as well as for measurement of haemoglobin.

It also aims to provide such a haematological-analysis reagent in the form of a single reagent and not in the form of a system of reagents.

It aims, moreover, to provide such a haematological-analysis reagent that does not comprise cyanic compounds.

Furthermore, the invention aims to provide such a haematological reagent that is quite particularly suitable for automated haematological instruments.

To this end, the invention proposes a haematological-analysis reagent of the type defined above, which essentially comprises:

- a buffer system that is suited to adjust selectively the pH of the reagent to an acidic value, in particular to a value lower than 3;
- at least one detergent of cationic type; and
- a nitrogenous compound.

The buffer system of the reagent is a key constituent, for the pH of the reagent permits identification of the subpopulation constituted by the basophil cells, which are of particular interest.

5

In fact, on account of their biochemical characteristics the basophil cells are capable of resisting the aggressivity of an acidic pH for a longer time than the other leucocytic subpopulations. This property therefore permits their isolation and their identification, notably by a resistive measurement.

10

The buffer system is advantageously chosen so that the pH value of the reagent is lower than 3 and preferably equal to 2.4.

15

The buffer system is advantageously chosen from the following:

20

- potassium chloride / hydrochloric acid;

- tartaric acid / sodium hydroxide;

- citric acid / sodium hydroxide;

25

- potassium hydrogen phthalate / hydrochloric acid;

- citric acid / disodium hydrogen phosphate; and

30

- boric acid / citric acid / potassium dihydrogen phosphate.

The detergents of cationic type fulfil a function of lysis of the red corpuscles or erythrocytes, permitting

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- liberation of the haemoglobin, which afterwards can be determined by measurement of absorbance. Generally speaking, the ionic detergents (anionic and cationic) are mainly used in order to dissociate the proteinic complexes and to solubilise the proteins of the membranes. They are also known as denaturants. Their action is rapid and therefore compatible with the rate-constraints specific to automated instruments.
- 10 The detergent is advantageously chosen from the following compounds:
- the primary amines, the acetates and hydrochlorides of fatty amines;
  - 15 - the quaternary ammonium salts and trimethylethylammonium bromide;
  - the amides of substituted diamines, cationised by ethyl sulfate, diethanolaminopropylamine or
  - 20 diethylaminopropylamide; and
  - the amides of cyclised diethylenetriamine.
- 25 The nitrogenous compound essentially fulfils a function of physicochemical stabilisation of the by-products of oxidation of haemoglobin.
- This nitrogenous compound is advantageously a thiourea, in particular 1,3-dimethyl-2-thiourea.
- 30

The reagent of the invention may comprise, moreover, at least one inorganic salt.

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This salt, if it is present, intervenes in the detergent activity and permits the phenomena of osmosis at the level of the cellular membranes to be maintained within the limits of normality, which is important for determination of the basophil cells. This salt also plays a role in the methods for measuring resistivity which are generally applied in automated haematological instruments.

The inorganic salt is advantageously constituted by an alkali-metal salt. The chlorides or sulfates of sodium or potassium may principally be cited as usable salts.

In preferred manner the detergent is present in a concentration of 0.2-20 g/l and the nitrogenous compound is present in a concentration of 0.1-10 g/l.

#### **Brief description of the drawings.**

Figure 1 is a graph showing values of measurements for the reagent of a preferred embodiment of the invention in comparison with a reference reagent,

Figure 2 is graph resulting from the reesistive analysis of a blood sample with a reagent according to the invention, and

Figure 3 is a graph showing the values of haemoglobin concentrations obtained by a reference reagent and by a reagent according to the invention.

#### **Description of preferred embodiment.**

The invention will now be described with reference to the following non-limiting example.

EXAMPLE

A haematological-analysis reagent is prepared from the compounds stated below and in the concentrations indicated:

5		Compounds	Concentrations
		potassium chloride	5-10 g/l
10		1,3-dimethyl-2-thiourea	0.5-3 g/l
		dodecyltrimethylammonium chloride	0.5-5 g/l
		potassium hydrogen phosphate / HCl	1.0-10 g/l

15 The above compounds are mixed, and the pH is adjusted to an acidic value lower than 3, typically of the order of 2.4.

With the aid of this reagent, haematological analyses are  
 20 carried out in respect of a sample of whole human blood, using an automated haematology instrument.

In order to do this, 10 µl of the sample of whole blood are brought into contact with 2 µl of the above reagent at  
 25 35°C.

Various types of analysis are carried out by comparing the reagent of the invention with one or more reference reagents.

30 The reference reagent is a lysing agent which is used in automated haematological instruments in order to reproduce the dosage of haemoglobin according to the classical, non-

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automated methodology, so-called Drabkin methodology. It is a matter of the dosage of cyanomethaemoglobin.

According to this method, ferrous iron ( $\text{Fe}^{++}$ ) of the haem of the haemoglobin, oxyhaemoglobin and carboxyhaemoglobin contained in the red corpuscles is oxidised to ferric iron ( $\text{Fe}^{+++}$ ) by iron cyanide so as to form methaemoglobin. Methaemoglobin then combines with the cyanide ions so as to form cyanomethaemoglobin which is measured by spectrophotometry at 540 nm [Drabkin, J. Biol. Chem. 112:51 (1935)].

On the other hand, the reagent of the invention is used in a dosage mode without cyanide. The erythrocytic haemoglobin is eluted by the action of an appropriate lysis agent. The haemic iron of the eluted haemoglobin is oxidised by the combined action of the erythrocytolytic compound and of the oxygen which is dissolved in the solution. The free methaemoglobin is unstable in comparison with cyanomethaemoglobin. Use is therefore made of compounds having electron-donor atoms, in order to reduce the haemic iron and to stabilise the methaemoglobin.

The reagent of the invention is used for various types of analysis which are performed in an automated haematological instrument.

1) Numeration of the leucocytes

A count of the total leucocytes or white corpuscles is carried out.

The results of measurement obtained with the reagent of the invention and those obtained with a reference reagent that

does not permit even partial leucocytic differentiation are compared.

Figure 1 shows the values of measurements expressed in thousands of cells, on the one hand for the reference reagent which is represented on the abscissa, and on the other hand for the reagent of the invention which is represented on the ordinate.

- 10 The graph shows an excellent correlation between the two types of measurement. The values of the correlation coefficient ( $R^2 = 0.99$ ) and of the slope of the straight regression line (0.99) indicate a very good correlation.

15 2) Differentiation and numeration of the basophil polymorphonuclear leucocytes

Figure 2 shows the curve resulting from the resistive analysis of a sample of whole blood with the reagent of the invention that was described above. This curve represents a histogram of distribution of the cells according to their size.

- 25 The x-axis (abscissa) corresponds to the determination of the cellular volumes ( $\mu\text{m}^3$ ) which are calculated by a resistive measurement. The basophil polymorphonuclear leucocytes are situated to the right of the central cursor (BAS). Located to the left of this central cursor are all the other leucocytic subpopulations, which cannot be
- 30 differentiated volumetrically by reason of the high aggressivity of the pH of the reagent.

In the example, basophil polymorphonuclear leucocytes are identified which represent a proportion of 6.2 % (by volume) in relation to the total leucocytic population.

5 3) Measurement of haemoglobin

A measurement of haemoglobin is performed with the reagent of the invention, and the results of measurements of the haemoglobin concentration with the reagent of the invention  
10 and with a reference reagent containing cyanic compounds are compared.

Figure 3 shows the values of haemoglobin concentrations (expressed in grams/litre) obtained by the reference  
15 reagent (representation on the abscissa) and by the reagent of the invention (representation on the ordinate). There too, the values of the correlation coefficient ( $R^2 = 0.99$ ) and of the slope of the straight regression line (1.09) indicate a very good correlation.

20 Thus the invention provides a single reagent that permits determination of leucocytes, identification of a leucocytic subpopulation (in particular, the basophil polymorphonuclear leucocytes) and measurement of  
25 haemoglobin, without using cyanic compounds.

The reagent of the invention presents, notably, the distinctive feature of permitting measurement of haemoglobin under very acidic conditions in relation to the  
30 known reagents.

Furthermore, this reagent comes in the form of a single reagent and not in the form of a system of several

reagents, and it is quite especially suitable for analyses that are performed in automated haematological instruments.

Of course, the invention is not limited to the embodiment  
5 example described previously but extends to other  
embodiment variants.

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Claims

1. A reagent for determination of leucocytes and of basophil polymorphonuclear leucocytes as well as for measurement of haemoglobin in a sample of blood, comprising:
- a buffer system that is suited to adjust selectively the pH of the reagent to an acidic value, in particular to a value lower than 3;
  - at least one detergent of cationic type;
  - a nitrogenous compound.
2. The reagent of Claim 1, wherein the buffer system is suited to adjust the pH to a value equal to 2.4.
3. The reagent according to Claim 1 wherein the buffer system is selected from the group comprising:
- potassium chloride / hydrochloric acid;
  - tartaric acid / sodium hydroxide;
  - citric acid / sodium hydroxide;
  - potassium hydrogen phthalate / hydrochloric acid;
  - citric acid / disodium hydrogen phosphate; and
  - boric acid / citric acid / potassium dihydrogen phosphate.

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4. The reagent of Claim 1, wherein the detergent is selected from the group comprising:

- the primary amines, the acetates and hydrochlorides of  
5 fatty amines;

- the quaternary ammonium salts and trimethylethylammonium bromide;

10 - the amides of substituted diamines, cationised by ethyl sulfate, diethanolaminopropylamine or diethylaminopropylamide; and

- the amides of cyclised diethylenetriamine.

15

5. The reagent of Claim 1, wherein the nitrogenous compound is a thiourea.

6. The reagent of Claim 5 wherein the thiourea is 1,3-  
20 dimethyl-2-thiourea.

7. The reagent of Claim 1, further comprising at least one inorganic salt.

25 8. The reagent of Claim 7, wherein the inorganic salt is an alkali-metal salt.

9. The reagent of Claim 7, wherein the inorganic salt is selected from the group comprising chlorides and sulfates  
30 of sodium or potassium.

10. The reagent of Claim 1, wherein the detergent is present in a concentration of 0.2-20 g/l and the



nitrogenous compound is present in a concentration of 0.1-10 g/l.

11. The reagent of Claim 1, having the following  
5 composition:

	Compounds	Concentrations
10	potassium chloride	5-10 g/l
	1,3-dimethyl-2-thiourea	0.5-3 g/l
	dodecyltrimethylammonium chloride	0.5-5 g/l
15	potassium hydrogen phosphate / HCl	1.0-10 g/l

**Abstract of the disclosure**

The invention concerns a reagent for determination of leucocytes and measurement of haemoglobin in a sample of blood. This reagent comprises a buffer system that is  
5 suited to adjust selectively the pH of the reagent to an acidic value, at least one detergent of cationic type, a nitrogenous compound and, optionally, at least one inorganic salt. This reagent can be used in haematological analyses in human medicine and also permits the  
10 identification of a leucocytic subpopulation, in particular the basophil polymorphonuclear leucocytes.

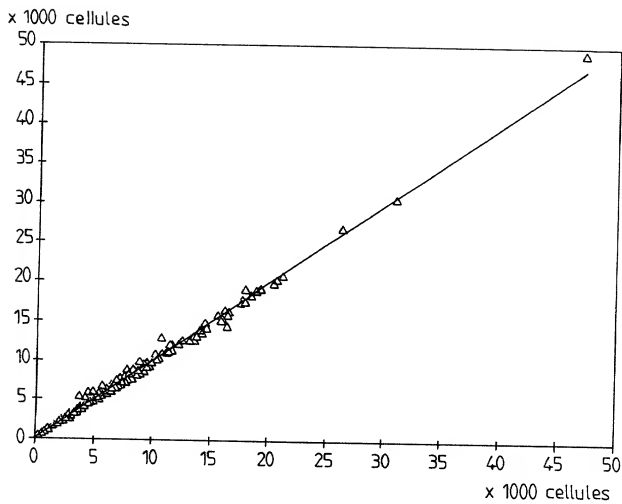


FIG.1

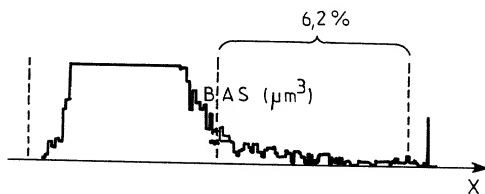


FIG.2

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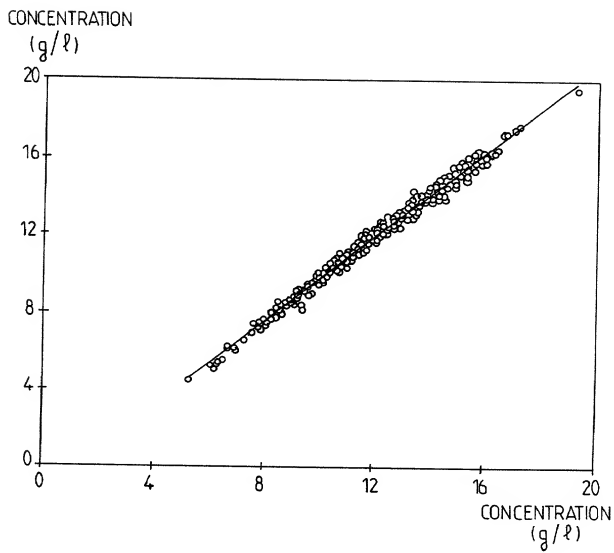


FIG.3

# DECLARATION FOR PATENT APPLICATION

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.  
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **Reagent for determination of leucocytes and measurement of haemoglobin in a sample of blood**  
the specification of which: (check one)

☒ is attached hereto. ☐ was filed on 19, as United States Patent Application Serial No. or PCT International Application Number                     , and was amended on 19 (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with 37 CFR § 1.56(a).  
Prior Foreign Application(s). I hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate listed below, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Priority Claimed

**99 03467**  
\_\_\_\_\_  
(Application No.)  
\_\_\_\_\_  
(Application No.)

**FRANCE**  
\_\_\_\_\_  
(Country)  
\_\_\_\_\_  
(Country)

**19/03/99**  
\_\_\_\_\_  
(Day/Month/Year Filed)  
\_\_\_\_\_  
(Day/Month/Year Filed)

☒ [ ]  
Yes No  
[ ] [ ]  
Yes No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date
_____	_____
_____	_____

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by 35 U.S.C. § 112, first paragraph, I acknowledge the duty to disclose material information as defined in 37 CFR § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(U.S. Application Serial No.)  
\_\_\_\_\_  
(U.S. Application Serial No.)

(U.S. Filing Date)  
\_\_\_\_\_  
(U.S. Filing Date)

(Status—patented, pending, abandoned)  
\_\_\_\_\_  
(Status—patented, pending, abandoned)

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Inventor's Signature

Date

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